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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,249	12/17/2001	Manuel Vega	119365-00002 / 911	7196

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EXAMINER	
LIN, JERRY	

ART UNIT	PAPER NUMBER
1631	

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10/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/022,249	VEGA ET AL.	
	Examiner	Art Unit	
	JERRY LIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,14,15,17-19,22-33,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,14,15,17-19,22-33,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 7, 2008 has been entered.

Status of the Claims

Claims 1-3, 5-8, 14, 15, 17-19, 22-33, 43, and 44 are under examination.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-3, 5-8, 14, 15, 17-19, 22, 23, 27, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. (US 5,223,409) in view of Wells et al. (US 6,013,478) and in view of Pedersen et al. (WO01/32844).

The instant claims are drawn to a method of producing a plurality of separate sets of nucleic acid molecules where each set of nucleic acid molecules differ from another set of nucleic acid molecules by one codon and the protein encoded on each set differ by one amino acid from the protein encoded on another set. The nucleic acid molecules are then introduced into host cells and an addressable array of these host cells is created where the location of each host cell and nucleic acid molecule is known. The host cells express the proteins and the proteins are individually screened to identify which proteins have a predetermined property that is a chemical, physical, or biological property or activity.

Regarding claims 1, 22, 23, and 42, Wells et al. teach a method of producing a plurality of separate sets of nucleic acid molecules that encode modified forms of a target protein (page 6, paragraph 45-65), where a residue substituted DNA sequence encodes a residue substituted polypeptide where each polypeptide contains a single substitution at a different amino acid within each segment of a protein (Wells describes proteins as being comprised of segments) (i.e. where each protein encoded by a nucleic

acid molecule set differs from the other proteins by only one amino acid and where the amino acid residues are replaced along the full-length) (column 6, lines 44-65, column 15, line 51-column 16, line 11); expressing the encoded proteins (column 13, lines 36-53); and screening the encoded proteins for a predetermined property that differs from the target protein by at least a 100% change (i.e. two-fold increase or decrease in Kd as compared to the parent protein) (column 17, lines 29-43); identifying each mutated protein as a hit and a designated hit position (i.e. active amino acid residues) (column 17, lines 29-43). Furthermore, Wells et al. teach modifying the nucleic acid molecules that encode the hits to produce more nucleic acid molecules by replacing codons in a hit position to produce nucleic acid molecules that differ by at least one codon (i.e., proteins that differ by one amino acid residue) (column 15, lines 50-11; column 17, lines 44-60); introducing the nucleic acid molecules into cells and screening the proteins for a predetermined activity (column 13, lines 36-53; column 17, lines 29-43; column 18, lines 25-43).

Although, Well et al. teach individually introducing a nucleic acid molecule into a host cell where the identity of the nucleic acid molecule is known (column 13, lines 36-53), Wells et al. do not teach creating an array of the host cells.

Regarding claims 1, Pedersen et al. teach a method of creating an array of host cells in a spatial array so that each location is occupied by a cell (abstract; page 37, lines 24-35); expressing the encoded protein (page 37, lines 24-35; page 40, lines 16-24); individually screening each encoded protein for a predetermined property that his a chemical, physical or biological property or activity (page 43, line 30-page 45, line 6).

Regarding claims 2 and 10, Wells et al. disclose where the nucleic acid molecules are individually designed and synthesized (column 13, lines 23-36; column 14, lines 40-63).

Regarding claims 3, 5, and 6, Pedersen et al. teach wherein each cell is deposited at a locus on a solid support in an addressable array (abstract; page 37, lines 24-35) that comprises a solid support with loci containing or retaining cells (e.g. micorotiter plate) (page 37, lines 19-23).

Regarding claims 7, 8, and 27, Wells et al. teach wherein the vectors may be plasmids or viral vectors (i.e. phase particles) (column 14, lines 12-29); and where the host cells are bacterial cells or eukaryotic cells (column 13, lines 26-63). Furthermore, Wells et al. teach modifying the nucleic acid molecules that encode the hits to produce more nucleic acid molecules by replacing codons in a hit position to produce nucleic acid molecules that differ by at least one codon (i.e., proteins that differ by one amino acid residue) (column 15, lines 50-11; column 17, lines 44-60); introducing the nucleic acid molecules into cells and screening the proteins for a predetermined activity (column 13, lines 36-53; column 17, lines 29-43; column 18, lines 25-43).

Regarding claims 14, 15, 43, and 44, Wells et al. teach where the pre-selected codon may encode any of the 19 naturally occurring amino acids (column 16, Table II).

Regarding claim 17, Wells et al. teach that after identifying two or more active amino acid residues (i.e. identifying nucleic acid molecules encoding the leads) (column 15, line 50-column 16, line 11; column 17, lines 35-60; column 17, lines 60-10), the parent nucleic acid molecule may be modified to reflect these two or more active amino

acid residues (i.e. recombining the nucleic acid molecules encoding the leads) (column 17, line 60-column 18, line 10), introducing the nucleic acid molecules into cells (column 13, lines 36-53); and screening the cells to identify nucleic acid molecules that encode new leads that exhibit a greater change in property or activity (column 18, lines 17-24).

Regarding claims 18 and 19, Wells et al. disclose where there are two or more leads (column 15, line 50-column 16, line 11; column 17, lines 35-60; column 17, lines 60-10); where the recombining is done via sit-direct mutagenesis (column 14 ,lines 40-63).

It would have been obvious to one of ordinary skill in the art to use the addressable arrays of Pedersen et al. with the method of Wells et al. Wells et al. teaches introducing nucleic acids into host cells for the purposes of producing modified proteins. In order to screen the different types of proteins, one of ordinary skill in the art would have been motivated to use a high-throughput method as taught by Pederson et al. to gain the advantage of a practical and reliable method for the identification of novel substances with new properties from a large number of molecules (page 37, lines 19-24). Thus one of ordinary skill in the art would have been motivated to combine the method so Wells et al. and Pedersen et al.

Response to Arguments

4. Applicants have responded to this rejection by stating that the previous application of Ladner et al. did not teach the limitations as claimed and was not combinable with Wells et al. The Examiner agrees and has withdrawn the Ladner et al.,

however, the remaining combination of Wells et al. and Pedersen et al. do teach the claim limitations. Applicants first respond to Wells et al. that Wells et al. does not teach a high throughput method because they study proteins individually. However, the instant claims contain no limitation of a high throughput method. In addition, the claims study each target protein individually by creating modified proteins, which is similar to the method taught by Wells et al.

Applicants also state that Wells et al. do not teach the further step of replacing the amino acids of each hit loci to identify amino acids that confer a desired change in activity. However, Wells et al. teach that once the amino acid position is identified, other amino acids may be substituted into that position (column 15, line 65-column 17, line 60).

Applicants have responded to the Pedersen et al. by stating that the clones used in the array are not known or identified. Because the clones are not known, the array is not addressable. However, the Examiner was not relying on Pedersen et al. to teach known clone cells, rather the Examiner was relying on Pedersen et al. to teach the used of a spatial array that may be used as an addressable array when combined with Wells et al. Wells et a. do teach individually introducing nucleic acids into a host cell (column 13, lines 36-53). Pedersen et al. demonstrates how these host cells may be grown in an addressable array.

5. Claims 24, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wells et al. (US 6,013,478) in view of Pedersen et al. (WO01/32844), as applied to

claims 1-3, 5-8, 14, 15, 17-19, 22, 23, 27, 43 and 44 above, and further in view of Berlioz et al. (US 5,925, 565).

The instant claims are drawn to a method of producing a plurality of separate sets of nucleic acid molecules where each set of nucleic acid molecules differ from another set of nucleic acid molecules by one codon and the protein encoded on each set differ by one amino acid to another protein encoded on another set. The nucleic acid molecules are then introduced into host cells and an addressable array of these host cells is created where the location of each host cell and nucleic acid molecule is known. The host cells express the proteins and the proteins are individually screened to identify which proteins have a predetermined property that is chemical, physical, or a biological property or activity. In particular, the instant claims include using eukaryotic cells or assessing the titer of viral vectors.

Wells et al. and Pedersen et al. are applied as above.

However, Wells et al. and Pedersen et al. do not teach assessing the titer of viral vectors.

Berlioz et al. teach assessing the titer of viral vectors after transfection for each set of eukaryotic cells (column 14, lines 39-65), and where the viral vector encodes for a protein involved in viral replication (column 5, lines 35-65).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the methods taught by Wells et al. and Pedersen et al. with Berlioz et al. in order to study the effects of the protein in an eukaryotic setting. Berlioz et al. teaches a method that allows eukaryotic cells, such as a human cell, to express a

desired protein (column 6, lines 5-22) for the purpose of producing a therapeutic treatment (column 7, lines 15-25). Wells et al. and Pedersen et al. methods teach screening for different proteins that exhibit a desired biological, chemical, or physical property. Thus one of ordinary skill in the art seeking to create a new therapeutic treatment, would be motivated to use Wells et al. and Pedersen et al. methods to design a product and use Berlioz et al.'s method to express the protein in an eukaryotic cell.

Response to Arguments

6. Applicants have responded to this rejection by stating Ladner et al., Wells et al., and Pedersen et al. do not teach all the limitations of the independent claims and Berlioz et al. does not cure this defect. See above for the Examiner's response.

7. Claims 25, 26, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wells et al. (US 6,013,478) in view of Pedersen et al. (WO01/32844) in view of Berlioz et al. (US 5,925, 565) as applied to claims 1-3, 5-8, 14, 15, 17-19, 22, 23, 27, 43 and 44 above, and further in view of Drittanti et al. (Gene Therapy (2000) Volume 7, pages 924-929)

The instant claims are drawn to a method of producing a plurality of separate sets of nucleic acid molecules where each set of nucleic acid molecules differ from another set of nucleic acid molecules by one codon and the protein encoded on each set differ by one amino acid to another protein encoded on another set. The nucleic acid molecules are then introduced into host cells and an addressable array of these host cells is created where the location of each host cell and nucleic acid molecule is

known. The host cells express the proteins and the proteins are individual screened to identify which proteins have a predetermined property that is chemical, physical, or a biological property or activity. In particular, the instant claims are drawn to a method of determining the titer using real time virus titer and tagged replication and expression enhancement.

Wells et al. Pedersen et al., and Berlioz et al. are applied as above.

Wells et al., Pedersen et al. and Berlioz et al. do not teach real-time virus titering or tagged replication and expression enhancement.

Drittanti et al. teaches real time virus titering (page 925); using tagged replication and expression enhancement (page 926, right column); and where the process is automated and computer controlled (page 925, left column under Figure 1).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the methods of Wells et al., Pedersen et al., and Berlioz et al. with Drittanti et al. to gain the benefit of determining the effectiveness of viral vectors. Berlioz et al. teach that one of his goals is to create an effective and stable viral vector (column 1, lines 10-17). Part of their method requires that they assess the titer of the viral vectors after transmission. Drittanti et al.'s method provides further insight into the stability and efficacy of the vector by offering real time titering. Thus one of ordinary skill in the art would be motivated to combine the methods of Wells et al. Pedersen et al., and Berlioz et al. with Drittanti et al. in order to gain the benefit of assessing the stability and efficacy of viral vectors.

Response to Arguments

8. Applicants have responded to this rejection by stating Ladner et al., Wells et al., and Pedersen et al. do not teach all the limitations of the independent claims and Drittanti et al. does not cure this defect. See above for the Examiner's response.

9. Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wells et al. and Pedersen et al., as applied to claims 1-3, 5-8, 14, 15, 17-19, 22, 23, 27, 43 and 44 above, and further in view of Persson et al. (Journal of Virology (1985) Volume 54, pages 92-97).

The instant claims are drawn to a method of producing a plurality of separate sets of nucleic acid molecules where each set of nucleic acid molecules differ from another set of nucleic acid molecules by one codon and the protein encoded on each set differ by one amino acid to another protein encoded on another set. The nucleic acid molecules are then introduced into host cells and an addressable array of these host cells is created where the location of each host cell and nucleic acid molecule is known. The host cells express the proteins and the proteins are individually screened to identify which proteins have a predetermined property that is chemical, physical, or a biological property or activity. In particular, the instant claims use Hill analysis.

Wells et al. and Pedersen et al. are applied as above.

However, Wells et al. and Pedersen et al. do not teach using Hill Analysis.

Persson et al. teach a method that uses the Hilll analysis (i.e. Hill coefficient) for determining the rate in which host cells are infected with viruses (abstract, page 94) or

fitting an output signal to a cure representative of a target protein and a test compound (page 94).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Wells et al. and Pedersen et al. with the method of Persson et al. to gain the benefit of determining if the plasmids or vectors are infecting the host cells. Wells et al. teach creating host cells with desired nucleic acids. In such a method, it would be desirable to determine the rate of infection in order to determine how to structure an experiment (e.g., incubation times, concentration, etc.). Persson et al. provide a method of determining the rate of infection. Thus one of ordinary skill in the art would be motivated to combine the methods of Wells et al. and Pedersen et al. with the method of Persson et al. to gain the benefit of determining the rate of infection of host cells to structure his experiments.

Response to Arguments

10. Applicants have responded to this rejection by stating Ladner et al., Wells et al., and Pedersen et al. do not teach all the limitations of the independent claims and Persson et al. does not cure this defect. See above for the Examiner's response.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JERRY LIN whose telephone number is (571)272-2561. The examiner can normally be reached on 7:00-5:30pm, M-TH.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jerry Lin/
Examiner, Art Unit 1631
10/13/08